(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 524 579 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **92112371.7**

(22) Date of filing: **20.07.92**

(51) Int. Cl.5: **A61K 31/70**, A61K 33/10, A61K 33/08, A61K 33/06, A61K 9/00, A61K 9/20

(30) Priority: **22.07.91 US 733547**
13.05.92 US 882204

(43) Date of publication of application:
27.01.93 Bulletin 93/04

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE

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(54) Improved oral dosing formulations of dideoxy purine nucleosides.

(57) Improved oral dosage formulations for acid-labile dideoxy purine nucleoside derivatives such as ddA, ddI, and ddG, have been developed by incorporating selected water-insoluble buffering systems in the formulation. These novel formulations provide reduced mass dosage units in the form of convenient, palatable chewable/dispersible tablets or a dry powder sachet. The reduced mass requirement, necessary to allow tablets of reasonable size, was achieved in part by an unexpected 20 to 25% increase in drug bioavailability resulting from use of the selected buffering systems comprised of an insoluble magnesium antacid agent and either dihydroxyaluminum sodium carbonate or calcium carbonate.

BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions which provide convenient, palatable oral dosage formulations for the acid-labile dideoxy purine nucleosides such as 2',3'-dideoxyadinosine, 2'3'-dideoxyinosine, and 2',3'-dideoxyguanosine. More specifically, it relates to inclusion of specific antacid buffers which confer special advantages such as increased bioavailability, lower variability in bioavailability between patients, greater convenience, lessened potential for gastrointestinal distress, and higher patient acceptability.

Compositions containing 2',3'-dideoxyadenosine (ddA), 2'3'-dideoxyinosine (ddl), and 2'3'-dideoxyguanosine (ddG), and their triphosphates for treating retroviral infections have been disclosed. Mitsuya, et al., in U.S. 4,861,759 disclose the oral administration of these dideoxy purine nucleosides in the form of liquids or tablets containing antacid buffering agents so that the pH of the resultant composition is in the neutral (pH6-pH8) range. Specifically exemplified and claimed is an oral gavage formulation containing 0.1 N acetate buffer with a pH of 6.8 to 7.2. Enteric coating of the tablets is also disclosed as an option.

The acid lability of the 2',3'-dideoxypurine nucleosides is well-known in the art and for that reason their oral administration typically requires administration on an empty stomach after ingestion of antacids. Prevention of acid-catalyzed hydrolysis of parent drug is important for these agents because their potent antiviral activity is lost in their hydrolysis by-products. Approaches to improving the acid stability of these acid-labile nucleoside derivatives have involved enteric-coated formulations, inclusion of a buffer in the pharmaceutical dosage form, and neutralization of the gastrointestinal tract just before drug ingestion by pretreatment with commercial antacids such as Maalox® or Mylanta®. Studies reported by McGowan, et al. in Reviews of Infectious Diseases, Vol. 12, Supp. 5, 5513-521 (1990) indicated that for ddl a superior approach for oral administration involves formulation of the drug at selected dose levels in combination with a fixed amount of citrate-phosphate buffer as a powder mixture. This dry mixture is enclosed in foil to provide a sachet (the "CP sachet") that must be mixed and diluted with liquid before oral ingestion.

Formulation approaches involving enteric coatings were not promising. Enteric coatings tended to reduce the nucleoside drug's bioavailability and depress its peak plasma levels. High peak plasma levels of active drug are an important requirement for its clinical antiviral activity. Enteric coated formulations also were especially susceptible to a meal effect, further reducing bioavailabilty.

The citrate-phosphate buffered ddl formulations, which allow oral dosing, were preferred clinically for long-term therapy over the earlier available lyophilized dosage form of the drug which also required reconstitution prior to intravenous administration. These oral powder formulations for reconstitution consist of varying ddl levels combined with the same amount of buffering ingredients (about 10 g. per day) regardless of final drug dose strength. All dose strength formulations thus have the same acid neutralization capacity. However, the powder blend sachets are bulky (about 20g/dose) and inconvenient - their use causes some patient inconvenience. Reconstitution is always required prior to administration and results in a large volume of constituted solution (due to 20 g. of solute) to be ingested. This salty solution can cause diarrhea and the required ingestion of about ten grams per day of soluble antacid buffers may result in systemic alkalosis when administered on a long-term basis as required, for example, in treating HIV infections.

A comparison of available oral formulations of ddl was recently reported (Hartman, et al., "Pharmacokinetics of 2',3'-dideoxyinosine in patients with severe human immunodeficiency infection. II. The effects of different oral formulations and the presence of other medications", Clin. Pharmacol. Ther. 1991; 50:278-85). With the maximum bioavailability of any buffered preparation being reported as ≤40%, the reference concludes that "a optimal preparation remains to be found." Of existing formulations, the "CP sachet" appeared to be the best oral preparation although its use caused reported diarrhea and/or hypokalemia in some patients.

It was an object of the present invention to provide improved pharmaceutical compositions for these acid-labile nucleoside derivatives which would allow convenient oral administration of reduced mass dosage formulations such as tablets that could be chewed and swallowed or readily dispersed in liquid for ingestion. Such compositions would also allow formulation of reduced mass sachet dosage forms.

Another objective was to combine selected antacid buffers in a fashion so that diarrhea and/or electrolyte and pH imbalances would be minimized.

A further object of the invention was to provide a pleasant tasting composition with high levels of patient acceptance and tolerability. A key to realization of these objects was in providing in a reduced mass form the same amount of bioavailable drug delivered by the bulky dry powder blend provided in the citrate-phosphate buffer sachets. Surprisingly, the improved buffer systems comprising certain water-insoluble aluminum or calcium carbonates in combination with water-insoluble magnesium antacids were found to

increase drug bioavailability by about 20 to 25%. Development of compatible sweetening and flavoring agents for incorporation into the improved drug-buffer composition also contributed to achieving the objects of the invention.

Summary of the Invention

Improved pharmaceutical compositions have been discovered which allow the oral administration of the acid-labile dideoxy purine nucleoside derivatives in the form of reduced mass powder sachets and preferably as convenient palatable chewable tablets. These tablets are also readily dispersible in liquids to offer an optional route of ingestion. Successful tablet formulation resulted from selection and development of compatible water-insoluble antacid buffer systems, which when combined with sweetening agents, flavoring agents, and other optional excipients deliver drug at a higher bioavailabilty than realizable in previous oral formulations, thereby permitting presentation in the more convenient and acceptable reduced mass form of a sachet or a chewable/dispersible tablet.

Detailed Description of the Invention

The present invention concerns an improvement in oral dosage formulations of acid-labile dideoxy purine nucleoside derivatives, e.g. ddA, ddl, and ddG. This formulation improvement concerns incorporation of the active drug ingredient in a reduced mass acid buffer formulation which can be provided as convenient palatable tablets that can be chewed and swallowed or easily dispersed in appropriate non-acidic liquids and then ingested. Reduced mass powder formulations in sachet form are also intended.

In order to formulate these acid-labile drugs as reasonably-sized convenient chewable/dispersible tablets, a pharmaceutical composition was required that would provide sufficient bioavailable drug in a palatable but non-bulky form. It was discovered that use of certain insoluble antacid buffers in combination gave a buffer system which actually provided an increase of drug bioavailability with reduced variability in drug levels between human subjects, compared with previous oral formulations. In addition, the new combination antacid buffer systems have improved palatability and a lowered potential for diarrhea or constipation which commonly result from chronic administration of many antacid agents.

Water-insoluble buffers, as applied to antacid agents which may be used in the instant buffer system, include antacids which have slight water solubility as well as those which are generally insoluble. The combination buffer systems of this invention are, in general, comprised of mixtures of water-insoluble antacid magnesium compounds with dihydroxyaluminum alkali metal carbonates or calcium carbonate. Preferred mixtures comprise about one part of a water-insoluble antacid magnesium compound in combination with about 2 to 4 parts of a dihydroxyaluminum alkali metal carbonate or with about 1.5 to 3 parts of calcium carbonate which is most preferred.

The water-insoluble antacid magnesium compound can be selected from magnesium carbonate, magnesium carbonate hydroxide, magnesium hydroxide, magnesium oxide, magnesium phosphate (tribasic), and magnesium trisilicate; or a combination of these to comprise the magnesium antacid component. Magnesium oxide and magnesium hydroxide are preferred, with magnesium hydroxide being the most preferred compound. The dihydroxyaluminum alkali metal carbonates refer chiefly to dihydroxyaluminum potassium carbonate and dihydroxyaluminum sodium carbonate, which is preferred.

In some of the instant formulations a water-soluble antacid buffer, such as a phosphate or citrate salt, e.g. sodium citrate, may also be added. These soluble antacid buffers would be provided in a lesser amount, generally representing less than about a quarter of the total amount of buffer. The range of ratios of the insoluble aluminum and calcium antacid buffer agents, such as dihydroxyaluminum alkali metal carbonate and calcium carbonate, to the insoluble magnesium antacid buffer agent reflects a balance between the diarrhea-promoting characteristics of the magnesium component and the constipation-causing characteristics of the aluminum and calcium components. Additionally, the instant combinations provide superior acid neutralizing properties which are very important given the limited quantities of buffer that can be used due to weight restrictions for reduced mass formulations. Another feature of the improved combination antacid buffer systems concerns the resultant gastric acidity following administration. For the dideoxy purine nucleosides, a pH of about 5 would appear to be the lower limit below which the drugs undergo rapid acid-catalyzed hydrolysis. A desirable buffer system would therefore maintain the stomach pH above 5 for at least half an hour but preferably for about an hour. It may also be desirable, as with these new buffer systems, that the stomach pH not rise much above 5 in order to limit potential for physiologic pH imbalance (alkalosis) in the gastrointestinal tract. The combination antacid buffer systems of the present invention were selected initially based on results of an acid neutralization rate test which will be described

in greater detail *infra*.

The unique synergistic characteristics of the selected insoluble aluminum and/or calcium carbonate compounds of the new combination buffer systems are demonstrated by comparing the results obtained when aluminum hydroxide, a widely-used antacid, was substituted for the selected aluminum/calcium component of the new buffer combinations. The aluminum hydroxide-containing buffer system was inferior to the instant buffer systems as it gave increased acidic pH values when studied in an *in vitro* gastric secretion test, even when additional aluminum hydroxide suspension was added. In contrast, the use of dihydroxyaluminum sodium carbonate or calcium carbonate combined with an insoluble magnesium compound gave time-extended pH values in the desired range (above pH 5) when tested in the *in vitro* gastric secretion system, indicative of its more efficient acid neutralization.

Finally, the importance of the new improved combination buffer systems can be appreciated in terms of improved palatability. Selection of the insoluble antacid buffers comprising these novel pharmaceutical compositions provide superior acid neutralization capacity while having organoleptic properties which minimize the amounts of sweetening and flavoring agents required for palatability.

In similar fashion, as for the previous citrate-phosphate buffer dry powder sachet formulations, the water-insoluble antacid buffers are provided at a constant level, independent of the drug dose to be incorporated in the instant pharmaceutical compositions. The improved buffer systems of the new formulations reduce the total amount of antacid ingested daily (about 10 g) in prior clinical formulations to about 3 to 8 g daily in the reduced mass formulations, either sachets or chewable dispersible tablets at recommended dose levels. Due to the increased bioavailability of drug substance achieved in these new pharmaceutical compositions, less drug is required to give potencies equivalent to the previous "CP sachet" dosage forms. Clinically for ddI, two tablets formulated from the improved pharmaceutical compositions can be given in place of a sachet dose as shown in Table 1.

Table 1

Dose Equivalences of ddI Chewable/Dispersible Tablets To Citrate/Phosphate Buffer Sachets

Two 150 mg ddI tablets (300 mg) equivalent to a 375 mg sachet.

Two 100 mg ddI tablets (200 mg) equivalent to a 250 mg sachet.

Two 50 mg ddI tablets (100 mg) equivalent to a 167 mg sachet.

Three 25 mg ddI tablets (75 mg) equivalent to a 100 mg sachet.

As shown in Table 1, the dose weight of ddI may be reduced by about 20-25% when given in the new chewable/dispersible tablet formulations compared to the old "CP" sachet form.

The improved oral pharmaceutical compositions of this invention contain then from about 5 to 150 mg of a 2',3'-dideoxy purine nucleoside derivative such as ddA, ddI, and ddG per tablet and from about 10 to 300 mg per sachet unit. There is also provided in these compositions, sufficient antacid buffer comprised of a water-insoluble antacid magnesium compound in combination with a dihydroxyaluminum alkali metal carbonate or calcium carbonate; so that adequate antacid capacity is achieved by the ingestion of two tablets or one reduced mass sachet as a dose. Desired sweetener agent, flavor and tableting excipients as well as a water soluble antacid buffer may be incorporated. More detailed specification of the mixed water-insoluble antacid buffer systems as well as other ingredients that may be incorporated into these novel dideoxy nucleosidic pharmaceutical compositions is given in the specific embodiments described *infra*.

Another aspect of the present invention concerns the palatability of the oral tablet formulation. The taste characteristics of the water-insoluble antacid buffers selected for use in the present invention are such that their incorporation into the present pharmaceutical compositions facilitates the objective of tablet palatability

by reducing the demand for ingredients to mask the taste of the buffer system itself. A sweetener component was selected which is comprised of aspartame to which sucrose or sorbitol may be optionally added to enhance the palatability according to the specific antacid compounds selected for the final composition. In general, little if any sucrose is added when calcium carbonate is selected as an antacid buffer component. From about 2 to 5 parts of sucrose per part of aspartame is preferred when dihydroxyaluminum sodium carbonate is an ingredient.

Selection of flavoring agents also may be varied depending upon the specific antacid compounds being used. Taste tests were employed to obtain the best tasting flavored compositions. Wintergreen, orange and mandarin orange flavorings are preferred.

Other pharmaceutical additives may also be incorporated. Although traditional chewable tablets do not require a disintegrant, one may be incorporated into these compositions in order to insure rapid disintegration when dosing as a dispersion is intended, as well as a rapid rate of acid neutralization after oral administration. Commercial disintegrants such as Polyplasdone XL and Explotab may be used. Glidants, such as silicon dioxide, and lubricants, such as magnesium stearate, may also be incorporated optionally into the pharmaceutical compositions of the present invention. The use of these and other pharmaceutical excipients is well known in the art. Similarly the formulation process and tableting operations would be considered standard practice in the pharmaceutical art.

For clinical use, two chewable/dispersible tablets, having the selected strengths of drug per tablet deemed appropriate by the attending or prescribing medical practitioner, will be chewed thoroughly either together or in rapid succession. A rinse of about 4 oz. (120 ml) of non-acidic liquid such as water may also be given. Alternatively, the two tablets may be thoroughly dispersed in at least one ounce of water and the dispersion then taken orally. To improve palatability and/or provide a taste change, the aqueous dispersion can be doubled or tripled in volume by the addition of another liquid such as milk, flavored milk, or a fruit juice. These mixed dispersions may be stored for up to an hour at room temperature prior to ingestion.

The tablets or dispersion should preferrably be ingested on an empty stomach twice daily. This means at least 30 minutes before eating or 2 hours after eating. This dosing regimen is offered as a guide to clinical use with the realization that the practice of medicine is individualized and medical practitioners may depart from this general guide according to their treatment practice with individual patients. Similarly the level of drug to be administered will be that which the medical practitioner feels is appropriate for the patient being treated, taking into account severity of disease, age and condition of patient and other relevant medical parameters.

In summary, the improved pharmaceutical compositions developed for oral administration of the acid-labile dideoxy purine nucleosides give unexpectedly improved drug bioavailability, lower drug level variability between patients, and has better palatability relative to prior formulations. These characteristics allow the formulation of reduced mass sachets and chewable/dispersible tablet formulations with their increased convenience and patient preference. The greater patient convenience associated with the use of oral tablets is felt to have a beneficial effect on patient compliance with their drug regimen. To patients that might have problems in chewing or swallowing, the dispersibility of the tablets is a further advantage.

The following examples describe in detail test methods and procedures for preparation and use of pharmaceutical compositions and formulations of the present invention. It will be apparent to those skilled in the art that many modifications, both of methods and materials and amounts, may be practiced without departing from the purpose and intent of this disclosure. From the foregoing description and the following examples it is believed that one skilled in the art is able to use the invention to the fullest extent.

Example 1

Acid Neutralization Rate - Test Method

This test was developed to determine rate and duration of acid neutralization and to measure efficiency of the formulations to maintain the desired pH. This test was performed using a USP apparatus II dissolution assembly (paddle method). Into the dissolution vessel, 750 mL of purified water, USP was added and equilibrated to 37 ± 1 °C. Into this water, a calibrated pH probe was immersed, and 4.0 mL of 1.0 N HCl was added, and the paddle stirrer, set at 100 RPM, was started. The contents were allowed to stir for at least two minutes before addition of the test sample. Test samples were prepared by dissolving/dispersing the test sample in a sufficient volume of water. A Harvard Infusion/Withdrawal Pump (model 940) was set up with a 30 mL syringe filled with 0.8214 N HCl. The piston speed was adjusted to deliver 28 mL of solution per hour (23 mEq/hour). The test sample was added to the dissolution flask and the Harvard pump was started immediately. The solution container was rinsed with purified water, USP, and the volume was made

to 972 mL. The media pH was recorded at selected time intervals over a period of one hour.

Compositions and Formulations

The following examples of pharmaceutical compositions and formulations employ ddI (generically known as Didanosine) as the representative drug member of the acid-labile nucleosides. This is because ddI has been approved for use in treating AIDS patients. The other acid-labile nucleosidic drug agents, e.g. ddA and ddG, could be readily substituted for ddI in the compositions and formulations.

The pharmaceutical compositions comprise, as a powder blend, didanosine and a buffer system which is itself comprised of an insoluble magnesium antacid compound, e.g. magnesium hydroxide, combined with either calcium carbonate or an insoluble aluminum antacid compound, e.g. dihydroxyaluminum sodium carbonate. Sweeteners, flavors, and other desireable excipients used in powder blends, as well as a water-soluble antacid, e.g. sodium citrate, may also be components. These pharmaceutical compositions are then formulated into oral dosing forms such as an oral powder suspension or chewable/dispersible tablets.

Example 2

Oral Suspension Dosage Form (reduced mass sachet)

A preferred embodiment of a didanosine powder composition for an oral suspension dosage form is prepared as follows.
The following ingredients were weighed:

didanosine	7.6 Kg
magnesium hydroxide	14.0 Kg
dihydroxyaluminum sodium carbonate	42.0 Kg
sodium citrate dihydrate	12.0 Kg
sucrose powder	43.0 Kg
orange flavor	1.2 Kg

All ingredients are added in a tumbling type V-blender and then blended for 15 minutes. The blend is then milled through Fitzmill with hammers forward using #00 plate at medium chamber speed and medium feed rate. The milled material is blended again in tumbling type V-blender for 20 minutes. This bulk blend is then assayed for drug potency and content uniformity (found 378 mg didanosine/6.0 g powder weight and RSD of 0.9% for 10 samples with a range of 369.8 mg to 381 mg/6.0 g weight) and filled into unit dose foil packets using a Bartelt powder filling and sealing machine (model IMG-9). These foil packets will contain 6.0 g of didanosine oral suspension powder which has the following compositions (depending on desired drug strength).

Ingredient	Weight
didanosine	0.020 g to 0.375 g
magnesium hydroxide	0.700 g
dihydroxyaluminum sodium carbonate	2.100 g
sodium citrate dihydrate	0.600 g
sucrose powder	Q.S.
orange flavor	0.060 g
Net Weight	6.000 g*

*Prior Art sachets ("CP sachet") contain 20 g of powder blend.

Example 3

Chewable/Dispersible Oral Tablet

A preferred embodiment of a didanosine chewable/disperible tablet formulation is prepared as follows.

The following ingredients were weighed:

didanosine	2.083 Kg
magnesium hydroxide	7.500 Kg
dihydroxyaluminum sodium carbonate	22.500 Kg
sodium citrate dihydrate	5.000 Kg
aspartame	0.667 Kg
polyplasdone XL10	1.250 Kg
powdered sucrose	2.667 Kg
microcrystalline cellulose pH 101	6.500 Kg
silicon dioxide	0.625 Kg
natural wintergreen flavor	0.375 Kg
magnesium stearate (for compaction)	0.625 Kg

All ingredients are placed in a tumbling type V-blender and blended for 10 minutes. The blend is then milled through Fitzmill with knives forward, using 1B plate at medium chamber speed, and medium feed rate. The milled material is blended again in tumbling type V-blender for 10 minutes. The blend is slugged on twelve station Colton D3 tablet press. The slugs are milled through Fitzmill with knives forward, using #4 plate at slow chamber speed, and medium feed rate. The milled slugs are then passed through oscillators using 16 mesh wire screen. The resulting granules are placed in a tumbling type V-blender to which calculated amount of magnesium stearate 0.0125 g/2.9875 g of granulation weight, and blended for 7 minutes. This blend is then assayed for drug potency and content uniformity (found 126 mg didanosine /3.0 g granulation weight and RSD of 1.0% for 10 samples with a range of 124 mg to 128 mg/3.0 g granulation weight. The granulation is compacted into tablets on twelve station D3 rotary tablet press using 7/8" round, flat beveled edge punches. Tablets are compacted to hardness of 16-24 Strong Cobb Units to a target weight of 3.0 g/tablet.

These tablet formulations then have the following compositions (depending on desired drug strength).

Ingredient	Weight
didanosine	0.010 g to 0.150 g
magnesium hydroxide	0.4500 g
dihydroxyaluminum sodium carbonate	1.3500 g
sodium citrate dihydrate	0.3000 g
aspartame	0.0400 g*
polyplasdone XL10	0.0750 g
powdered sucrose	0.1600 g
microcrystalline cellulose pH 101	Q.S.
silicon dioxide	0.0375 g
natural wintergreen flavor	0.0225 g
magnesium stearate (for compaction)	0.0375 g
magnesium stearate (for tableting)	0.0125 g
Net Weight	3.00 g

*0.0600 g aspartame to be used for 150 mg didanosine tablets

Example 4

Sodium-Free Chewable/Dispersible Oral Tablet #1

A preferred embodiment of a sodium-free didanosine chewable/dispersible tablet formulation is prepared as follows.

didanosine	0.300 Kg
calcium carbonate	1.100 Kg
magnesium hydroxide	0.500 Kg
aspartame	0.120 Kg
polyplasdone XL10	0.150 Kg
silicon dioxide	0.040 Kg
microcrystalline cellulose	1.460 Kg
natural orange flavor	0.100 Kg
magnesium stearate (for slugging)	0.020 Kg
magnesium stearate (for tableting)	0.010 Kg

All ingredients are placed in a tumbling V-blender and blended for 10 minutes. The blend is then milled through Fitzmill with knives forward using #1 plate at medium chamber speed, and medium feed rate. The milled material is blended again in tumbling type V-blender for 10 minutes. The blend is slugged on single punch F-press. The slugs are milled through Fitzmill with knives forward, using #4 plate at slow chamber speed, and medium feed rate. The milled slugs are then passed through oscillator using 16 mesh wire screen. The resulting granules are placed in a tumbling type V-blender to which calculated amount of magnesium stearate 0.01 g/1.89 g of granulation weight and blended for 10 minutes. The blend is then compacted into tablets on single punch F-press using 3/4" round, flat beveled edge punches. Tablets are compacted to hardness of 18-21 strong cell units to a target weight of 1.9 g/tablet.

As an example, tablet formulations have the following composition.

Ingredient	Amount (g) Per Tablet
didanosine	0.005 to 0.150
calcium carbonate (light)	0.550
magnesium hydroxide	0.250
aspartame	0.020 to 0.060*
polyplasdone XL10	0.075
silicon dioxide	0.020
microcrystalline cellulose	q.s. (0.730)
natural orange flavor	0.050
magnesium stearate (for slugging)	0.010
magnesium stearate (for tableting)	0.005
Total Tablet Weight	1.900

*Amount of aspartame varies with didanosine content and intermediate strength compositions contain proportional amounts of aspartame.

Example 5

Sodium-Free Chewable/Dispersible Oral Tablet #2

A more preferred embodiment of a sodium-free didanosine chewable/dispersible tablet formulation can be prepared by appropriate modification of the procedure set forth in Example 4 to provide tablets having the following composition.

Ingredient	Amount (g) Per Tablet
didanosine	0.005 to 0.150
calcium carbonate (light)	0.550
magnesium hydroxide	0.250
aspartame	0.020 to 0.070*
polyplasdone XL10	0.100
sorbitol	0.300
microcrystalline cellulose	q.s. (0.600)
mandarin orange flavor	0.050
magnesium stearate (for slugging)	0.015
magnesium stearate (for tableting)	0.015
Total Tablet Weight	2.10

* Amount of aspartame varies with didanosine content.

Example 6

Evaluation of the Comparative Bioavailability of Didanosine Administration of 375 mg Dose as a Solution, Chewable Tablet and Suspension

Assessment of bioavailabilities of didanosine from two new formulations, a chewable tablet and a suspension, relative to that of a citrate/phosphate buffer solution, was conducted in 18 male subjects who were seropositive for the Human Immunodeficiency Virus (HIV). This study was performed in six subjects at each of the three clinical sites using an open randomized three-way crossover design. Each subject received a single 375 mg didanosine oral dose after an overnight fast. There was a 7-day washout period between each treatment. Serial blood samples and the total urinary output over 12 hours were collected and assayed for intact didanosine by validated HPLC assays. Pharmacokinetic parameters were calculated using noncompartmental methods. The mean parameters are listed below:

Formulation	CMAX (ng/ml)	TMAX* (hr)	MRT(INF) (hr)	T-HALF (hr)	AUC(INF) (hr.ng/ml)	CLR (ml/min)	%UR
C/P Buffer	1901	0.68	1.77	1.36	2851	507	21.9
Chewable Tablet	2364	0.50	1.86	1.37	3315	455	23.0
Suspension	2651	0.50	1.80	1.39	3574	477	26.4

TMAX*: median was reported.
CMAX - highest observed plasma concentration of drug.
TMAX - time elapsed to reach CMAX.
T-HALF - the drug elimination half-life.
AUC(INF) - the area under the drug concentration vs time curve, extrapolated to infinity.
MRT(INF) - mean residence time in the body, extrapolated to infinity.
CLR - renal clearance of drug.
UR - total urinary recovery.

The rate of absorption and elimination of these three formulations were essentially the same, based on the values of TMAX, MRT(INF) and T-HALF. The pharmacokinetic characteristics of didanosine remained unaltered regardless of the differences in formulation. The bioavailability estimates with 90% confidence limits for the chewable table relative to the citrate/phosphate buffer were 124% (106-135%) for CMAX and 116% (108-125%) for AUC(INF). The bioavailability estimates with 90% confidence limits for the suspension

relative to the citrate/phosphate buffer were 139% (121-154%) for CMAX and 125% (117-134%) for AUC(INF). Based on the 90% confidence interval approach, the two new formulations were more bioavailable than the reference formulation, citrate/phosphate buffer.

Example 7

Evaluation of the Comparative Bioavailability of Didanosine (2',3'-Dideoxyinosine, ddl) After Administration As A solution And As A Chewable Tablet

The bioavailability of a chewable tablet formulation of didanosine relative to the reference formulation, a citrate/phosphate buffer sachet, was evaluated in 24 male patients seropositive for the Human Immunodeficiency Virus. Using a randomized crossover study design, a single 375 mg oral dose of the citrate/phosphate buffer sachet or a 300 mg dose of the chewable tablet (administered as 2 x 150 mg tablets) was given under fasting conditions. The alternate treatment was given 1 week later. Serial blood samples and the total urinary output were collected over a 12 hr. interval after each dose. Plasma and urine samples were analyzed for didanosine using validated HPLC/UV methods. Concentration data were used to calculate pharmacokinetic parameters using noncompartmental methods. Mean (SD) values for key parameters are summarized below:

Formulation N=23	CMAX (ng/ml)	TMAX* (hr)	MRT(INF) (hr)	T-HALF (hr)	AUC(INF) (hr.ng/ml)	CLR (ml/min)	%UR (mg)
Citrate/ Phosphate	1595 (584)	0.75	2.35 (0.79)	1.76 (0.82)	2953 (838)	469 (160)	78.4 (26.7)
Chewable Tablet	1628 (548)	0.50	2.18 (0.59)	1.73 (1.03)	2571 (773)	433 (169)	64.2 (25.4)

*Median is reported.

There were no statistically significant sequence or period effects observed for any parameter, based on analysis of variance results. The bioavailability assessment of the chewable table formulation of didanosine relative to the citrate/phosphate buffer was made on the basis of the two one-sided tests procedure. The point estimate and 90% confidence interval for CMAX for the chewable tablet relative to the citrate/phosphate buffer sachet was 103% (95%, 112%). Corresponding values for AUC(INF) were 87% (81%, 93%). It is concluded that a 375 mg dose of didanosine, administered as the citrate/phosphate buffer is equivalent to a 300 mg dose of the chewable tablet.

Claims

1. A dideoxy purine nucleoside pharmaceutical composition adapted for oral administration and having improved bioavailability, the composition comprising from about 5 to 150 mg per dosing unit of a dideoxy purine nucleoside selected from 2',3'-ddA, 2',3'-ddI, and 2',3'-ddG, and salts and/or hydrates thereof; and an effective amount of a water-insoluble antacid buffering composition which is comprised of a water-insoluble antacid magnesium compound combined with a dihydroxyaluminum alkali metal carbonate or calcium carbonate.

2. A dideoxy purine nucleoside pharmaceutical composition adapted for oral administration and having improved bioavailability, the composition comprising:

   from about 5 to 150 mg per dosing unit of a dideoxy purine nucleoside selected from 2',3'-ddA, 2',3'-ddI, and 2',3'-ddG, and salts and/or hydrates thereof; and

   an effective amount of a water-insoluble antacid buffering composition which further comprises about

   about one part of a water-insoluble antacid magnesium compound in combination with about 2 to 4 parts of a dihydroxyaluminum alkali metal carbonate or with about 1.5 to 3 parts of calcium carbonate.

3. The composition of Claims 1 or 2 wherein the water-insoluble antacid magnesium compound is selected from the group consisting of magnesium carbonate, magnesium carbonate hydroxide, magnesium hydrate, magnesium oxide, magnesium phosphate (tribasic), and magnesium trisilicate.

4. The composition as claimed in Claims 1 to 3 further comprising one or more ingredients selected from the group consisting of a water-soluble antacid buffer, a sweetening agent, a flavoring agent, a disintegrant, a binder, and pharmaceutically acceptable excipients, carriers or diluents.

5. The composition of claim 1 comprising 2',3'-ddI, calcium carbonate, magnesium hydroxide and further comprising a sweetening agent, a flavoring agent and pharmaceutically acceptable excipients.

6. A chewable/dispersible oral tablet formulation comprising the pharmaceutical composition as claimed in Claims 1 to 5.

7. An oral powder formulation intended for dispersal in a liquid and comprising the pharmaceutical composition as claimed in Claims 1 to 5.

8. A chewable or dispersible tablet formulation comprising from about 25 to 150 mg of 2',3'-ddI; about 1.3 to 1.4 g of dihydroxyaluminum sodium carbonate; about 0.4 to 0.5 g of magnesium hydroxide; about 0.3 g of sodium citrate dihydrate; about 0.06 g aspartame and about 0.16 g sucrose; about 0.075 g Polyplasdone XL10; about 0.04 g silicon dioxide; about 0.02 g wintergreen flavor; about 0.05 g magnesium stearate; and sufficient microcrystalline cellulose to yield a tablet weighing about 3.0 g.

9. A chewable or dispersible tablet formulation comprising about 25 to 150 mg of 2',3'-ddI; about 0.5 to 0.6 g calcium carbonate; about 0.2 to 0.3 g magnesium hydroxide; about 0.06 g aspartame; about 0.08 Polyplasdone XL10; about 0.02 g silicon dioxide; about 0.05 g orange flavor; about 0.02 g magnesium stearate and sufficient microcrystalline cellulose to yield a tablet weighing about 1.9 g.

10. A chewable or dispersible tablet formulation comprising about 25 to 150 mg of 2',3'-ddI; about 0.5 to 0.6 g calcium carbonate; about 0.2 to 0.3 g magnesium hydroxide; about 0.07 g aspartame; about 0.1 Polyplasdone XL10; about 0.03 g sorbitol; about 0.05 g mandarin orange flavor; about 0.03 g magnesium stearate and sufficient microcrystalline cellulose to yield a tablet weighing about 2.1 g.

11. A process for preparing a pharmaceutical composition or formulation according to anyone of claims 1 to 10 which comprises admixing the dideoxy purine nucleoside with the other ingredients and preparing the desired dosage form.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 11 2371

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	US-A-4 260 596 (MACKLES L.) 7 April 1981 * column 6; example 4 *	1-7,11	A61K31/70 A61K33/10 A61K33/08 A61K33/06 A61K9/00 A61K9/20
Y	SCIENCE vol. 245, 28 July 1989, pages 412 - 416 YARCHOAN R. ET AL 'IN VIVO ACTIVITY AGAINST HIV AND FAVORABLE TOXICITY PROFILE OF 2'3'-DIDEOXYINOSINE' * page 412, column 3, paragraph 3 - page 413, column 1, paragraph 2 *	1-7,11	
Y	EP-A-0 138 540 (SMITH KLINE DAUELSBERG GMBH) 24 April 1985 * page 8 - page 9; examples 6,7 * * claims 1,9 *	1,3,4,7, 11	
Y	GB-A-2 082 456 (BRISTOL MYERS COMPANY) 10 March 1982 * page 4 - page 5; example 1 *	1-4,11	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A	WO-A-8 802 629 (AMERICAN HEALTH PRODUCTS CORPORATION) 21 April 1988 * page 5; example V * * claim 1 *	1	A61K
A	WO-A-9 109 605 (THE UNITED STATES OF AMERICA (THE SECRETARY US DEPARTMENT OF COMMERCE)) 11 July 1991 * claims 22-30 *	1	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	04 NOVEMBER 1992	BOULOIS D.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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